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attyn Paper 12

Declaration of Paul Chinn, Ph.D.

I, PAUL CHINN, hereby declare and state as follows:

1. I am currently employed at IDEC Pharmaceuticals as a Senior Scientist.

2. I was awarded a B.S. in Biochemistry from University of California (Los Angeles, California) in 1979.

3. I was awarded a M.S. in Biochemistry from California State University (Long Beach, California) in 1983.

4. I was awarded a Ph.D. in Chemistry from University of California (San Diego, California) in 1987.

5. I have conducted research in the fields of protein modification and development of protein therapies during the past 15 years. My expertise encompasses antibody-based therapies for canine heartworm disease, vaccine development for the treatment of feline leukemia, drug targeting strategies for cancer therapy, and radioimmunotherapy. I continue to work in these areas.

6. I have carefully reviewed U.S. Patent No. 5,942,210 to Ultee et al. ("Ultee"), which issued on November 15, 1994. I understand that Ultee was cited as prior art in an Office Action issued from the U.S. Patent and Trademark Office, which is dated October 18, 2002, in association with U.S. Serial No. 09/628,186 ("the '186 application" or "the present application"), on which I am a named inventor. It is my further understanding that the Examiner who is handling prosecution of the present application is of the belief that the "one pot" method for radiolabeling a lyopholized protein, as described by Ultee, anticipates claims 1-3, 5, 17, and 19 of the present application. I respectfully disagree with this interpretation, as described below.

7. The one pot radiolabeling methods of Ultee involve labeling of a lyophilized conjugate/transchelator/reducing agent mixture via addition of a solution containing the isotope.

^{99}Tc-labeled antibodies having high specific activity were prepared by this method and administered to test animals, apparently without a prior purification step. Ultee suggests, but does not show, that the disclosed one pot radiolabeling method can be used to prepare radiolabeled therapeutic pharmaceuticals using ^{186}Re, ^{188}Re, and ^{189}Re.

8. Based on my expertise, I disagree with the suggestion of Ultee that the one pot method can be used to prepare therapeutic radioconjugates. Specifically, it is my opinion that the conjugation chemistries used to perform the one pot radiolabeling method are incompatible with the use of high energy β-emitters typically employed for therapeutic applications. I believe that radiolabeling of a protein using ^{186}Re, ^{188}Re, and ^{189}Re, or other hi energy β-emitters, when the labeling is performed according to the one pot method of Ultee, will result in rapid radiolysis of the labeled protein. This radiolysis would be particularly evident using Re isotopes, which typically require harsher conditions (elevated temperature and increased incubation time) for attachment to an antibody. An explanation of the different labeling conditions when using Tc versus Re isotopes can be found in Cancer Therapy with Radiolabeled Antibodies, edited by David M. Goldenberg, CRC Press, 1995 (*see* chapters 6 and 7). Therefore, based on my substantial expertise in radiolabeling methods, I believe that the method of Ultee, which employs chemistry for the labeling of ^{99m}Tc, would not provide >95% radioincorporation with a therapeutically relevant Re isotope as suggested.

9. The Examiner contends that the linker molecule used in the methods of Ultee is equivalent to the chelator used in the methods of the present application. This conclusion is incorrect. In the cited passages of Ultee, a linker molecule is identified as having the dual function of (1) binding a radioisotope to the targeting molecule, and (2) protecting the chemical reducing agent from oxidation. Ultee, at col. 14, lines 21-27. Ultee also states that hydrazyl

pyridine derivatives and substituted thioureas are preferred linker molecule classes. Ultee, at col. 14, line 27 through col. 16, line 32. These are weak chelators, which may be sufficient for chelation of low energy isotopes such as ^{99}Tc, but which are subject to catabolism and release of high energy metallic isotopes such as ^{90}Y. Ultee does not disclose or suggest the use of linker molecules that mediate stable chelation of high energy metallic isotopes, including rhenium isotopes and particularly yttrium isotopes.

10. In contrast to the linker molecules of Ultee, representative chelators used in accordance with the present invention include MX-DTPA, phenyl-DTPA, benzyl-DTPA, and CHX-DTPA (page 12, lines 1-5). These DTPA derivatives have been modified to promote facile labeling kinetics and improved stability on binding to high energy metallic isotopes. DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) similarly shows improved stability of high energy radioconjugates and can therefore also be used in accordance with the present inventive methods. The stability of radiolabeled pharmaceuticals is critical because free high energy radioisotopes (*i.e.*, radioisotopes that have been released following catabolism of the chelator) show deleterious accumulation in bone.

11. Base on the foregoing statements, a linker molecule of Ultee is not equivalent to a chelator as used in the present inventive methods. In addition, it is my belief that the one pot radiolabeling methods of Ultee cannot be used to prepare therapeutic radiopharmaceuticals that can be directly administered to a patient.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: March 26, 2003

Paul Chinn, Ph.D.